ECG changes at rest and during exercise in lowlanders with COPD travelling to 3100 m

Carta, Arcangelo F ; Bitos, Konstantinos ; Furian, Michael ; Mademilov, Maamed ; Sheraliev, Ulan ; Marazhapov, Nuriddin H ; Lichtblau, Mona ; Schneider, Simon R ; Sooronbaev, Talant ; Bloch, Konrad E ; Ulrich, Silvia

Abstract: BACKGROUND The incidence and magnitude of cardiac ischemia and arrhythmias in patients with chronic obstructive pulmonary disease (COPD) during exposure to hypobaric hypoxia is insufficiently studied. We investigated electrocardiogram (ECG) markers of ischemia at rest and during incremental exercise testing (IET) in COPD-patients travelling to 3100 m. STUDY DESIGN AND METHODS Lowlanders (residence <800 m) with COPD (forced volume in the first second of expiration (FEV_1) 40-80% predicted, oxygen saturation (SpO_2) 92%, arterial partial pressure of carbon dioxide ($PaCO_2$) <6 kPa at 760 m) aged 18 to 75 years, without history of cardiovascular disease underwent 12-lead ECG recordings at rest and during cycle IET to exhaustion at 760 m and after acute exposure of 3 h to 3100 m. Mean ST-changes in ECGs averaged over 10s were analyzed for signs of ischemia (1 mm horizontal or downsloping ST-segment depression) at rest, peak exercise and 2-min recovery. RESULTS 80 COPD-patients (51% women, mean ± SD, 56.2 ± 9.6 years, body mass index (BMI) 27.0 ± 4.5 kg/m^2, SpO_2 94 ± 2%, FEV_1 63 ± 10% prEd.) were included. At 3100 m, 2 of 53 (3.8%) patients revealed 1 mm horizontal ST-depression during IET vs 0 of 64 at 760 m (p = 0.203). Multivariable mixed regression revealed minor but significant ST-depressions associated with altitude, peak exercise or recovery and rate pressure product (RPP) in multiple leads. CONCLUSION In this study, ECG recordings at rest and during IET in COPD-patients do not suggest an increased incidence of signs of ischemia with ascent to 3100 m. Whether statistically significant ST changes below the standard threshold of clinical relevance detected in multiple leads reflect a risk of ischemia during prolonged exposure remains to be elucidated.

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Arcangelo F. Carta [a], Konstantinos Bitos [a], Michael Furian [a], Maamed Mademilov [b], Ulan Sheraliev [b], Nuriddin H. Marazhapov [b], Mona Lichtblau [a], Simon R. Schneider [a], Talant Sooronbaev [b], Konrad E. Bloch [a], Silvia Ulrich [a,*]

[a] Department of Respiratory Medicine, University Hospital Zurich, Switzerland
[b] Department of Respiratory Medicine, National Center for Cardiology and Internal Medicine, Bishkek, Kyrgyzstan

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ABSTRACT

Background: The incidence and magnitude of cardiac ischemia and arrhythmias in patients with chronic obstructive pulmonary disease (COPD) during exposure to hypobaric hypoxia is insufficiently studied. We investigated electrocardiogram (ECG) markers of ischemia at rest and during incremental exercise testing (IET) in COPD-patients travelling to 3100 m.

Study design and methods: Lowlanders (residence <800 m) with COPD (forced volume in the first second of expiration (FEV_1) 40–80% predicted, oxygen saturation (SpO_2) ≥92%, arterial partial pressure of carbon dioxide ($PaCO_2$) <6 kPa at 760 m) aged 18 to 75 years, without history of cardiovascular disease underwent 12-lead ECG recordings at rest and during cycle IET to exhaustion at 760 m and after acute exposure of 3 h to 3100 m. Mean ST-changes in ECGs averaged over 10s were analyzed for signs of ischemia (≥1 mm horizontal or downsloping ST-segment depression) at rest, peak exercise and 2-min recovery.

Results: 80 COPD-patients (51% women, mean ± SD, 56.2 ± 9.6 years, body mass index (BMI) 27.0 ± 4.5 kg/m^2, SpO_2 94 ± 2%, FEV_1 63 ± 10% prEd.) were included. At 3100 m, 2 of 53 (3.8%) patients revealed ≥1 mm horizontal ST-depression during IET vs 0 of 64 at 760 m ($p = 0.203$). Multivariable mixed regression revealed minor but significant ST-depressions associated with altitude, peak exercise or recovery and rate pressure product (RPP) in multiple leads.

Conclusion: In this study, ECG recordings at rest and during IET in COPD-patients do not suggest an increased incidence of signs of ischemia with ascent to 3100 m. Whether statistically significant ST changes below the standard threshold of clinical relevance detected in multiple leads reflect a risk of ischemia during prolonged exposure remains to be elucidated.

1. Introduction

Due to increasing worldwide mobility and advances in infrastructure, a considerable number of patients with chronic obstructive pulmonary disease (COPD) travel to high altitude. However, the safety of altitude sojourns in COPD-patients is insufficiently known. COPD-patients have a higher prevalence of cardiovascular diseases [1–4], including coronary artery disease (CAD) which may predispose to cardiac ischemia in a hypoxic environment. The body physiologically adapts to altitude with increased breathing- and heart rates causing a shortening of the diastole [5]. As cardiac perfusion mainly occurs during diastole, the risk of cardiac ischemia may increase with altitude due to the reduced cardiac perfusion relative to increased myocardial oxygen consumption. COPD-patients also have a lower respiratory reserve compared to healthy, who use an increased breathing rate as a compensatory mechanism at altitude. COPD-patients additionally may reveal pulmonary hypertension already at low altitude, but even more in a hypoxic environment at high altitude, which further strains the right ventricular reserve to ischemia, due to increased load [6,7]. The mentioned adaptive responses are accentuated during exercise.

Abbreviations: AV, Atrioventricular; BMI, Body mass index; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; ECG, Electrocardiogram; FEV_1, Forced expiratory volume in the first second of expiration; FVC, Forced vital capacity; GOLD, Global initiative for chronic obstructive lung disease; HCO^{3-}, Hydrogencarbonate; IET, Incremental exercise testing; LVH, Left ventricular hypertrophy; PAC, Premature atrial contraction; $PaCO_2$, Arterial partial pressure of carbon dioxide; PaO_2, Arterial partial pressure of oxygen; PQ, PQ interval; PVC, Premature ventricular contraction; QRS, QRS complex duration; QT, QT interval; QTc, Corrected QT interval; RPP, Rate pressure product; RVH, Right ventricular hypertrophy; SpO_2, Saturation of oxygen.

* Corresponding author at: Head of Pulmonary Hypertension, Clinic of Pulmonology, University Hospital of Zurich, Rämistrasse 100, 8091 Zürich, Switzerland.
E-mail address: silvia.ulrich@usz.ch (S. Ulrich).

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The electrocardiogram (ECG) is a well-established and widely available tool to diagnose scars and cardiac ischemia at rest and during exercise. There are various studies on ECG-changes at altitude in healthy subjects [8] but to date there are very few studies on ECG-changes in COPD-patients exposed to hypoxia at real or simulated altitude, especially during exercise [9]. One study showed that during a high altitude simulation test (up to 3048 m) 2 out of 22 patients with normocapnic COPD developed asymptomatic premature atrial or ventricular contractions (PAC and PVC) [10]. Recent studies detected a significant increase of nocturnal PVC in patients with moderate to severe COPD at 2500 m [11] or showed a significant increase in nocturnal corrected QT interval (QTc) in COPD-patients at 2048 m, which wasn't affected by supplementary oxygen [12]. However, to our knowledge, no study has yet investigated signs of ischemia or arrhythmia on a 12-lead ECG in COPD-patients who travel to and perform exhaustive exercise at high altitude. Thus, we investigated ECG-changes at rest and during incremental exercise testing (IET) in COPD-patients travelling to 3100 m with focus on signs of ischemia.

2. Methods

2.1. Study design and participants

This is a nested study within a larger ongoing clinical trial investigating structured self-monitoring for early signs of altitude related adverse health events during an altitude sojourn in COPD-patients. This study was conducted in accordance with the amended Declaration of Helsinki. The ethics committee of the National Center for Cardiology and Internal Medicine in Bishkek, Kyrgyzstan approved the trial and all subjects provided written consent.

Male and female lowlanders born, raised and currently living at <800 m with moderate to severe COPD (GOLD 2&3, forced expiration volume in the first second of expiration (FEV_1) 40–80% predicted; oxygen saturation (SpO_2) ≥92%; arterial pressure of carbon dioxide ($PaCO_2$) <6 kPa at 760 m) between 18 and 75 years were included in this study. Exclusion criteria were acute COPD-exacerbations, severe COPD with hypoxemia or hypercapnia on ambient air at 760 m, history or symptoms of severe cardiovascular disease, such as CAD, or any disease interfering with protocol compliance, including heavy smoking (>20 cigarettes per day).

Subjects underwent baseline measurements during an initial two-day visit in Bishkek at 760 m. After a break at home (3–21 days) subjects returned to Bishkek, where baseline resting ECG and IET were performed. On the next day, they were transferred by mini-bus to an altitude clinic at 3100 m (Tuja Ashu, Kyrgyzstan). ECG at rest and during IET were performed after 3 h at altitude.

2.2. Measurements

Trained study personnel obtained all measurements. At the first visit, detailed personal history, physical examination and current medication were obtained. Age, height, weight, body mass index (BMI), blood pressure, heart rate, breathing rate and SpO_2 were recorded. Participants performed spirometry (Spirostik, Diffustik, Geratherm, Geschwenda, Germany) according to the 2005 American Thoracic Society/European Respiratory Society guidelines [13]. Radial artery blood gases were drawn and immediately analyzed (RapidPoint 500, Siemens, Zurich, Switzerland).

12-lead resting ECGs were recorded electronically at 760 and 3100 m (CardioPart 12 Blue, Amedtec, Aue, Germany). Subjects were asked to lie in a supine position for 5 min and the skin was cleaned and shaved before applying the electrodes. Participants performed IET on an electronically braked cycle ergometer (Ergoselect 100, Geratherm, Geschwenda, Germany) at 760 m and 3100 m. Predicted maximal workload was automatically calculated by the software dependent on age, gender and weight and the ramp was adjusted to achieve a test duration of 8–12 min. IET was preceded by 2 min of rest and followed by 2 min of recovery where patients were sitting on the bicycle. 12-lead ECG, heart rate and SpO_2 ($WristOx_2$ 3150, Nonin Medical Inc., Plymouth, Minnesota, USA) were continuously recorded and blood pressure obtained every two minutes.

2.3. 12-Lead ECG analysis

Resting ECGs at 760 m and 3100 m were categorized as normal or abnormal. ECGs were considered abnormal if they showed signs of prior ischemia (Q-waves, T-wave inversions), bundle branch blocks, signs of left or right ventricular hypertrophy (LVH or RVH), axis deviation, conductance disturbances, prolonged QTc (>450 ms in males and > 460 ms in females, using Bazett's formula [14]) or preexisting arrhythmia. PQ interval, QRS duration, and QT interval (PQ, QRS and QT) were measured electronically (ECGpro version 4.80.007, Amedtec GmbH, Aue, Germany).

In the exercise ECGs, three measurement time points were defined: at rest, at peak exercise and after 2 min of recovery. ST segment changes were averaged automatically over 10 s (minimum 7 QRS complexes) and measured electronically 80 ms after the J-point (or 60 ms in cases of early repolarization, after visual review by the investigators). PQ, QRS and QT were measured electronically. PAC and PVC scored manually. Single leads with significant artefacts were excluded from analysis. Two investigators categorized all resting ECGs and manually scored the exercise ECGs for signs of ischemia. Where opinions differed, consensus was reached by agreement.

2.4. Outcomes

The primary outcome was the difference in proportion of ECG-signs of clinically relevant ischemia at peak exercise (defined as ≥1 mm horizontal or downsloping ST-segment depression or new T-wave inversions) between 760 m and 3100 m. As the current study was nested within a larger trial with predetermined sample size according to a power calculation for that trial's primary outcome, no independent a priori sample size estimation for the analysis of ST-segment changes was performed. Nevertheless, an exploratory post-hoc assessment of power was carried out using the observed data.

Secondary outcomes included incidence of cardiac symptoms (chest pain, palpitations, headache, dizziness, syncope, nausea), arrhythmia, mean ST-changes in any lead, changes in QTc, PAC and PVC per minute during IET at 760 and 3100 m and the prevalence of abnormal resting ECGs as described above at 760 m and 3100 m.

2.5. Statistical analysis

Final analysis included all available measurements from 760 m and 3100 m. Single missing values of secondary outcomes were not replaced. All statistical analyses were performed using R Studio (version 1.2.1578, R Studio Inc., San Francisco, USA). Resting ECG parameters were compared with two-sided, paired *t*-tests. Resting ECG categorizations and incidences of ischemia during IET were compared using Fisher's exact or Chi-squared tests. Analyses of ST-segment changes, QTc, and PVC and PAC per minute were performed in a multivariable mixed linear regression model, with altitude (760 m vs 3100 m), time point (rest, peak exercise and 2-min recovery), sex (only for QTc), FEV_1 and rate pressure product (RPP, heart rate × systolic blood pressure) as independent variables. Single leads with significant artefacts are excluded from analysis. Continuous data are reported as mean ± standard deviation and parameters from the multivariable mixed linear regression models are expressed as mean change and 95% confidence interval. A *p*-value threshold of <0.05 or a confidence interval not crossing 0 was considered to be statistically significant.

3. Results

3.1. Study population

A total of 80 patients were included in the study, consisting of a near equal number of middle-aged men and women of normal weight, with moderate airflow obstruction and only mild hypoxemia at 760 m. Table 1 shows the baseline characteristics. Supplementary Fig. 1 shows the patient flow.

3.2. Resting 12-Lead ECG analysis

Resting ECG categorizations and indices at 760 m and 3100 m are presented in Table 2. All 80 patients performed resting ECG at 760 m, of which 52 (65%) were categorized as normal and 28 (35%) as abnormal. The most common abnormality on resting ECG at 760 m were signs of prior ischemia (16%), which presented almost exclusively in the inferior leads, followed by QTc-prolongation (15%) and first-degree atrioventricular (AV) block (5%). One patient with right bundle branch block was excluded from QT/QTc analysis. At 3100 m, 66 of 80 patients underwent resting ECG, of which 43 (65%) were categorized as normal and 23 (35%) as abnormal. As at 760 m, the most common abnormality detected were signs of previous ischemia (17%) again almost exclusively presenting in the inferior leads, followed by QT-prolongation (12%) and first-degree AV block (6%).

Abnormalities of resting ECGs seen at 760 m, including signs of prior ischemia and first-degree AV blocks, persisted at 3100 m, but were not different in proportion or severity. PQ, QRS and QTc did not differ significantly from 760 m to 3100 m. 3 subjects with previously borderline normal QTc at 760 m developed QTc-prolongation at 3100 m, whereas QTc normalized in 4 subjects. 14 subjects did not undergo resting ECG at 3100 m (Supplementary Fig. 1), of which 9 had normal ECGs at 760 m, 2 signs of previous ischemia in the inferior leads, 2 QTc-prolongation, and one right bundle branch block.

Table 1
Patients' baseline characteristics at 760 m.

Baseline characteristics	Mean ± SD or number (%)
Patient number	80
Men / women, n	39 (49%) / 41 (51%)
Age, years	56.2 ± 9.6
Height, cm	163 ± 9
Weight, kg	72.8 ± 14.2
BMI, kg/m^2	27.0 ± 4.5
Pulmonary function tests	
GOLD II / III	68 (85%) / 12 (15%)
FEV1, % predicted	63 ± 10
FVC, % predicted	87 ± 12
FEV1/FVC, %	57 ± 11
Vital parameters	
Blood pressure systolic, mmHg	122 ± 12
Blood pressure diastolic, mmHg	80 ± 9
Heart rate, min^{-1}	82 ± 11
Breathing rate, min^{-1}	19 ± 2
SpO_2, %	94 ± 2
Arterial blood gas analyses	
pH	7.49 ± 0.02
PaO_2, kPa	9.5 ± 1.0
$PaCO_2$, kPa	5.5 ± 0.5
HCO^{3-}, mmol/l	24.8 ± 2.2
Comorbidities	
Arterial hypertension	18 (23%)
Diabetes	5 (6%)
Medication	
None	19 (24%)
Inhaled beta-adrenergics	35 (44%)
Inhaled steroids	29 (36%)
Inhaled anticholinergics	31 (39%)
Antihypertensives	16 (20%)
Beta-blockers	4 (5%)
Antidiabetics	4 (5%)
Aspirin	11 (14%)
Oral steroids	0 (0%)

Data are reported as mean ± standard deviation (SD) or number and percentage (%). BMI: body mass index; FEV1: forced expiration in one second; FVC: forced vital capacity; SpO2: oxygen saturation by pulse oximetry; PaO2: arterial oxygen partial pressure; PaCO2: arterial carbon dioxide partial pressure; HCO3-: hydrogencarbonate

Table 2
Resting ECG at 760 m and 3100 m.

Resting ECG indices, ms	Bishkek (760 m)	Tuja Ashu (3100 m)	
	Mean ± SD	Mean ± SD	
QTc (males)	426 ± 21	430 ± 22	$p = 0.374$
QTc (females)	438 ± 20	438 ± 22	$p = 0.525$
QT (males)	387 ± 24	383 ± 22	$p = 0.131$
QT (females)	388 ± 20	386 ± 20	$p = 0.539$
PQ	162 ± 28	162 ± 28	$p = 0.814$
QRS	86 ± 10	88 ± 8	$p = 0.167$
Heart rate	82 ± 11	84 ± 12	$p = 0.143$

Resting ECG categorization	Bishkek (760 m)	Tuja Ashu (3100 m)	
	Number (%)	Number (%)	
Total ECGs	80	66	
Patients with normal resting ECG	52 (65%)	43 (65%)	
Patients with abnormal resting ECG	28 (35%)	23 (35%)	$p = 0.985$
Signs of prior ischemia	13 (16%)	11 (17%)	$p = 0.946$
of which inferior leads:	12 (15%)	10 (15%)	$p = 0.980$
of which anterior leads:	1 (1%)	1 (2%)	$p = 1.000$
Prolonged QTc interval	12 (15%)	8 (12%)	$p = 0.615$
of which male (>450 ms):	5 (6%)	4 (6%)	p = 1.000
of which female (>460 ms):	7 (9%)	4 (6%)	$p = 0.755$
1st degree AV block	4 (5%)	4 (6%)	p = 1.000
Right axis deviation	2 (3%)	2 (3%)	p = 1.000
Left ventricular hypertrophy	1 (1%)	1 (2%)	p = 1.000
Right bundle branch block	1 (1%)	0 (0%)	p = 1.000
Left anterior fascicular block	1 (1%)	1 (2%)	p = 1.000

Data are reported as mean ± standard deviation (SD) or number and percentage (%). Resting ECG indices and categorization did not differ significantly between 760m and 3100m. One patient with right bundle branch block was excluded from QT and QTc Interval analysis.

3.3. Exercise 12-Lead ECG analysis

64 out of 80 patients (80%) performed IET including 12-lead ECG at 760 m. Of the 64 patients with IET at 760 m, 53 patients (66% of total) performed IET at 3100 m (Supplementary Fig. 1). At 3100 m 2 (3.8%) patients with previously normal resting ECG revealed ≥1 mm ST-depression on exercise ECG vs 0 at 760 m ($p = 0.203$). One patient with ≥1 mm ST-depression reported chest pain. No patients developed clinically significant supraventricular or ventricular arrhythmia at 760 m or 3100 m. There were significant changes in peak workload, %-predicted workload, heart rate, RPP and SpO_2 at peak exercise between 760 m and 3100 m (Table 3).

In a multivariable mixed linear regression model, multiple ECG leads showed associations between mean ST-segment changes and altitude, time point and combined interaction between altitude, peak exercise and 2-min recovery (Fig. 1 and Supplementary Table 1). When adjusted for altitude and RPP, the model showed independent associations of RPP with mean ST-segment changes in multiple leads (Supplementary Table 2). However, there was no association between mean ST segment changes in any lead and baseline FEV_1. QTc showed an independent association with altitude (−6(−11 to −1) ms, $p = 0.022$)) but was independent of sex, FEV_1 and RPP. Single PAC and PVC were recorded in some individuals, but PAC and PVC per minute did not show an association with any of the independent variables.

Table 3
Incremental Exercise Testing at 760 and 3100 m.

Incremental exercise testing at peak exercise	Bishkek (760 m)	Tuja Ashu (3100 m)	
	Mean ± SD	Mean ± SD	
Peak workload, W	100 ± 28	92 ± 22	$p < 0.001$
Workload, % predicted	74 ± 14	68 ± 11	$p < 0.001$
Heart rate, min^{-1}	131 ± 16	139 ± 17	$p < 0.001$
Pulse oximetry, %	93 ± 5	83 ± 8	$p < 0.001$
Rate pressure product, $mmHg^{*}min^{-1}$	20,824 ± 5294	23,030 ± 5088	$p = 0.001$

Reasons for exercise abortion	Bishkek (760 m)		Tuja Ashu (3100 m)		
	Total n	With ECG signs of ischemia	Total n	With ECG signs of ischemia	
Total Exercise Tests	64	0	53	2 (4%)	$p = 0.203$
Fatigue	58 (91%)	0	44 (83%)	1 (2%)	
Blood pressure systolic >210 mmHg	2 (3%)	0	1 (2%)	0	
Blood pressure systolic decrease >20 mmHg	1 (2%)	0	0	0	
Chest pain	0	0	1 (2%)	1 (2%)	
Headache	1 (2%)	0	2 (4%)	0	
Palpitations	0	0	1 (2%)	0	
Nausea	0	0	1 (2%)	0	
Dizziness	1 (2%)	0	1 (2%)	0	
Syncope	0	0	0	0	
Severe cough	1 (2%)	0	0	0	
Leg or knee pain	0	0	2 (4%)	0	

Data are reported as mean ± standard deviation (SD) or number and percentage (%).

3.4. Post-hoc power calculation

An exploratory post-hoc assessment of the study's power to detect clinically relevant ST-segment changes of >1 mm was performed based on the number of 53 participants (after drop-outs), the observed SD of ST-changes of 0.27 mm, accounting for multiple testing in the 12 leads over the course of 5 repeated assessments by reducing the alpha level by a factor of 100 to 0.0005. This calculation revealed a power to detect ST-changes >1 mm of >99% and a power of 80% to detect ST-changes as small as 0.16 mm.

4. Discussion

This is the first study investigating ECG-signs of ischemia during cycle exercise in a large cohort of patients with COPD travelling to 3100 m. The main finding is that patients with moderate to severe COPD without resting hypercapnia and only mild hypoxemia at low altitude and no history of apparent CAD did not reveal a significantly higher incidence of ischemia during IET at 3100 m. However, a multivariable mixed linear regression analysis revealed significant ST-changes of unknown clinical relevance, associated with altitude, exercise and RPP, but not FEV_1. Additionally, we report a high prevalence of abnormal resting ECGs, most frequently signs of previous ischemia, QTc-prolongation and first-degree AV block, which persisted after 3 h at 3100 m. Resting ECG time indices did not change significantly at 3100 m, and there was no incidence of clinically relevant arrhythmia.

4.1. Resting 12-lead ECG analysis

COPD-patients frequently reveal cardiovascular comorbidities, even independently of shared risk factors [1–4] and those with markers of ischemia on ECG have increased risk of sudden cardiac death [15] and higher mortality [16]. The prevalence of markers of ischemia on resting ECG in COPD has been reported at 21% overall and at 14% in COPD-patients without self-reported cardiovascular disease [17] and are in line with the present study (16%), although we excluded patients with unstable CAD. These findings indicate that COPD-patients often reveal occult ischemic heart disease. Interestingly, the ischemic ECG-changes found in our collective presented almost exclusively in the inferior leads and may indicate right ventricular susceptibility to ischemia in COPD-patients. In comparison, a study by Warnier [18] showed an overall frequency of CAD of 19%, with a prevalence of 7% in inferior and 4% in anterior Q-wave myocardial infarctions. Chronically increased right ventricular load due to pulmonary hypertension at low altitude, but even more in a hypoxic environment at high altitude and during exercise [6,7], may contribute to right sided ischemia. However, in disagreement to these markers of ischemia, the only sign of chronic right ventricular strain [19] found in our collective was isolated right axis deviation in 3% and right bundle branch block in 1% of subjects. With 15%, the prevalence of QTc-prolongation in our study was higher than in Warnier's study (9%) [18] but lower than reported by Sievi (32%) [20], which is most probably due to different collectives with milder disease in the first, but more severe in the latter study. Accounting for disease severity, the frequency of QTc-prolongation found in our study is comparable with these previous reports [18,20].

4.2. Exercise 12-lead ECG analysis

To our knowledge, evidence on ischemic ECG-changes in COPD-patients at altitude is very scarce. A study by Graham [9] with repeated ECGs at rest and during treadmill exercise, showed 'no cardiac irregularities in 8 patients with moderate COPD during a three day sojourn at 1920 m. Other studies with ECG during simulated altitude [10] and during nights at altitude [11,12] did not report signs of ischemia. The presently investigated COPD-patients did not reveal a higher incidence of ischemia defined as horizontal or downsloping ST-segment depression ≥1 mm during IET at 3100 m compared to 760 m. However, in a mixed linear regression model, statistically significant ST-depression in relation to acute altitude exposure was predominantly detected in the lateral precordial leads, whereas significant ST-depression during exercise was predominantly detected in the inferior leads. Moreover, when adjusted for the RPP, the regression models showed a significant association with altitude in both the inferior and lateral precordial leads. Although the number of leads with exercise-induced ST-depression is associated with the size of ischemic area, it is not clear whether the region of affected ECG-leads reflect the location of cardiac ischemia [21]. Significant additive effects of exercise and altitude exposure on ST-depression, compared to the single factors exercise *or* altitude were also detected, again mostly in the lateral precordial leads (Fig. 1). Whether these significant but minor ST-changes reflect early signs of ischemia is unknown. One study reported that exercise-induced ST-depression in patients without known CAD did not predict future coronary events [22] but it is unclear whether the same applies for COPD-patients, who have increased risk of cardiovascular comorbidity. The presently investigated COPD-patients reached significantly lower absolute and %-predicted workloads at 3100 m compared to 760 m. On the other hand, they also attained significantly higher RPP and HR levels and lower SpO_2 levels at peak exercise at 3100 m, which may indicate that the ischemic stimulus was at least comparable at high altitude.

In contrast to COPD, several studies investigated exercise ECGs- in patients with CAD at altitude. A study by Levine showed that 10 out of 20 veterans with manifest or high risk for CAD revealed clinically relevant ST-depression upon acute exposure to 2500 m on resting ECG,

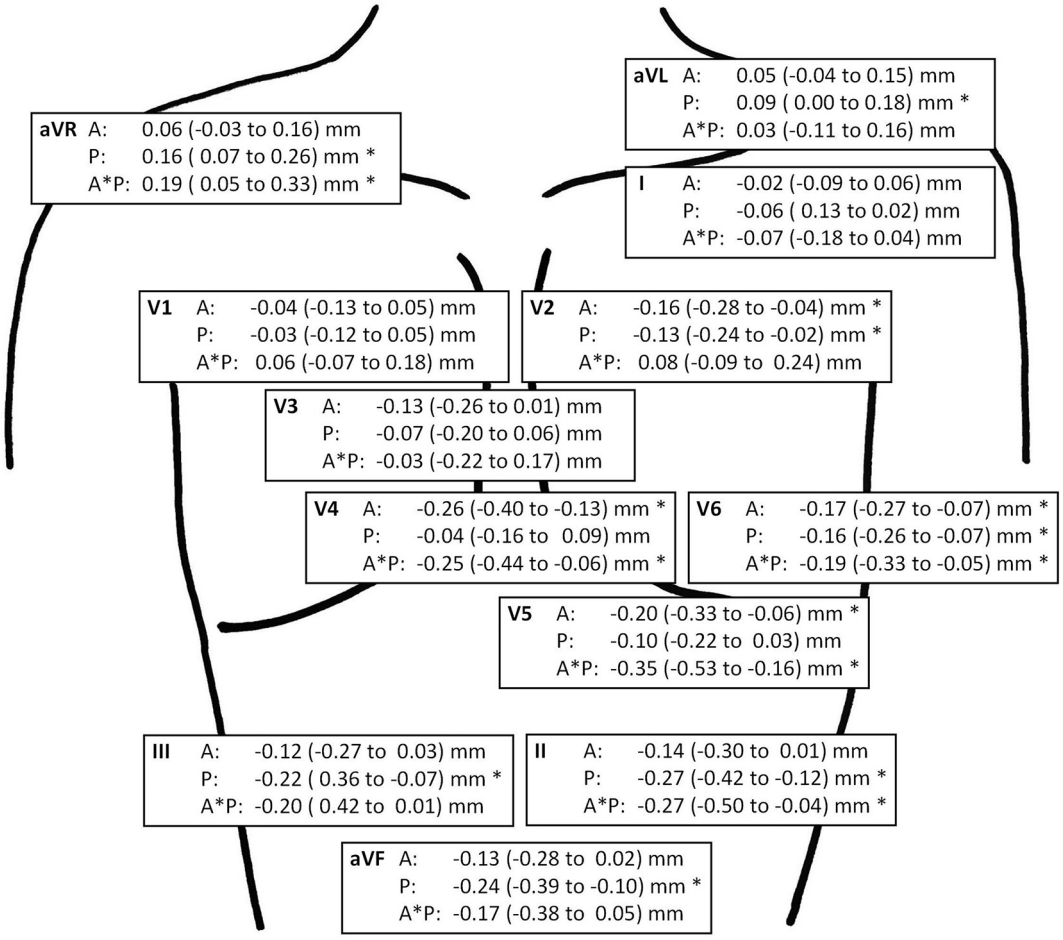

Fig. 1. Mean ST-segment changes at rest and during exercise: Mean ST-segment changes (95% confidence interval) at rest and during exercise are shown for each lead of a 12- ECG as calculated by multivariable mixed linear regression model with A: representing changes with altitude (from 760 m to 3100 m), P: changes from rest to peak exercise. A*P: represents the additive changes of peak exercise from rest at altitude (3100 m), Significant changes ($p < 0.05$) are denoted with *.

but not during exercise or after acclimatization, and echocardiography directly after exercise did not reveal new motion abnormalities at altitude [23]. A study in 22 low-risk CAD-patients revascularised after myocardial infarction and with normal IET at low altitude, did not reveal ischemia or arrhythmia during IET at 3500 m [24]. Accordingly, a literature review concluded that high altitude exposure in patients with stable CAD is relatively safe, with none of the studies reporting ischemia at rest or during exercise upon short-term exposure to moderate to high altitudes between 2500 and 3500 m [25]. Additionally, studies at varying levels of altitude in patients with arterial hypertension [26], metabolic syndrome [27] and congestive heart failure [28], all common comorbidities in COPD [1–4], did not report ischemic ECG-changes.

4.3. Arrhythmia and QTc interval

In healthy subjects, PAC and PVC constitute the most frequently reported arrhythmia at altitude but the relationship between PVC and life-threatening ventricular arrhythmia remains inconclusive [8]. It is well established that COPD-patients have increased cardiac arrhythmias [18,29–31], including supraventricular tachyarrhythmia such as atrial fibrillation, atrial flutter and multifocal atrial tachycardia [30] and the severity of COPD is independently associated with atrial fibrillation, non-sustained and sustained ventricular arrhythmia [30] independently of left ventricular function [31]. There are few reports on arrhythmia in COPD-patients at altitude, with the exception of increased nocturnal PAC and PVC at 2590 m [11]. In our study, we did not observe clinically relevant arrhythmias and occasional PAC or PVC were not increased with altitude or exercise, however, our total ECG-observation time was relatively short.

Prolonged QTc is considered a risk factor for ventricular arrhythmia, particularly for torsade de pointes [32]. QTc-prolongation has been observed in hypoxemic COPD-patients [33] and during acute COPD-exacerbation and was associated with increased mortality [34] and may be related to hypoxia [20]. Our study did not find a significant change of QTc from 760 m to 3100 m. Interestingly, in the multivariable mixed linear regression model, QTc duration even decreased at altitude independently of exercise. These findings contrast with a recent study by Bisang [12], which demonstrated a significant, albeit not clinically relevant QTc-prolongation during nocturnal measurements at 2048 m in a comparable COPD-patient collective. However, in that study [12] the duration of exposure to hypoxia was longer compared to our study. This may indicate that QTc-prolongation needs longer altitude exposure and/or is more frequently found during sleep. Nocturnal QTc-prolongation was also found in patients with obstructive sleep apnea at 2590 m [35]. In another study in patients with obstructive sleep apnea, endothelial dysfunction, presumably induced by intermittent hypoxia, was improved by nocturnal continuous positive airway pressure (CPAP) therapy [36].

Retrospective studies by Nilsson and Armstrong found associations between severity of COPD and QTc-prolongation [37,38] and frequency of ischemic changes on resting ECG [39]. In contrast, none of the ECG indices in our study, including QT and QTc, showed an association with exercise or disease severity as expressed by FEV_1.

4.4. Limitations

This study has the following limitations: we investigated COPD-patients at rest and IET three hours after arrival at 3100 m. Future studies might include repeated ECGs at rest and exercise during prolonged sojourns at high altitude to determine whether clinically significant ischemia develops. Some patients did not perform IET at 3100 m because they developed relevant hypoxemia or symptoms and descended back to 760 m according to safety criteria. This may have introduced a selection bias, as it is possible that these subjects would have manifested ischemia at rest or during IET. An exploratory post-hoc analysis revealed that this study was highly (>99%) powered to detect mean clinically relevant ST-changes of 1 mm and even powered with 80% to detect much smaller mean ST-changes of 0.16 mm. While our data may suggest that exposure to hypoxia at altitude did not induce significant myocardial ischemia in the studied patients as a group, we strongly caution against concluding that clinically relevant myocardial ischemia is unlikely to occur in an individual patient in the setting of our study. Nevertheless, our observations represent a valuable basis for designing future, much larger studies that will be required to evaluate the risks of cardiac ischemic events in COPD patients going to high altitude. Technical limitations included some unavoidable movement artefacts in the extremity leads, which led to exclusion of some leads in some individuals, and the dependency on the accuracy of the ECG software for the measurement and averaging of ECG indices over 10 s.

5. Conclusion

This study investigating ECG-changes at rest and during exercise in COPD-patients travelling to 3100 m did not reveal an increased incidence of signs of ischemia nor arrhythmia. However, statistically significant ST-depressions below the threshold of clinical relevance were detected in multiple leads. It remains to be investigated, whether these subclinical ST-depressions reflect early signs of ischemia and whether ST-changes would increase upon longer stays at altitude, upon exposure to higher altitude or in more severe COPD.

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Author contributions

SU[1] is the guarantor and takes responsibility for the content of the manuscript, including the data and analysis. AFC[1] contributed to acquiring, analyzing, and interpreting the data, writing and revising the article critically for important intellectual content and providing final approval of the version to be published. KB[1], MF[1], MM[2], US[2], NHM[2], ML[1] and SRS[1] contributed to data collection and analysis and revising the article critically for important intellectual content. TS[2], KEB[1] and SU[1] conceived the project and contributed to data collection, analysis, and interpretation, writing the manuscript, revising the article critically for important intellectual content, and providing final approval of the version to be published. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Declaration of Competing Interest

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References

[1] S.M. Curkendall, C. DeLuise, J.K. Jones, S. Lanes, M.R. Stang, E. Goehring, et al., Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients, Ann. Epidemiol. 16 (1) (2006) 63–70.

[2] S.P. Bhatt, M.T. Dransfield, Chronic obstructive pulmonary disease and cardiovascular disease, Transl. Res. 162 (4) (2013) 237–251.

[3] W. Chen, J. Thomas, M. Sadatsafavi, J.M. FitzGerald, Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis, Lancet Respir. Med. 3 (8) (2015) 631–639.

[4] J.R. Feary, L.C. Rodrigues, C.J. Smith, R.B. Hubbard, J.E. Gibson, Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care, Thorax. 65 (11) (2010) 956–962.

[5] R. Naeije, Physiological adaptation of the cardiovascular system to high altitude, Prog. Cardiovasc. Dis. 52 (6) (2010) 456–466.

[6] M. Lichtblau, T.D. Latshang, M. Furian, S. Müller-Mottet, S. Küest, F. Tanner, et al., Right and left heart function in lowlanders with COPD at altitude: data from a randomized study, Respiration. 97 (2) (2019) 125–134.

[7] M. Lichtblau, M. Furian, S.S. Aeschbacher, M. Bisang, S. Ulrich, S. Saxer, et al., Dexamethasone improves pulmonary hemodynamics in COPD-patients going to altitude: a randomized trial, Int. J. Cardiol. 283 (2019) 159–164.

[8] J.S. Windsor, G.W. Rodway, H.E. Montgomery, A review of electrocardiography in the high altitude environment, High Alt. Med. Biol. 11 (1) (2010) 51–60.

[9] W.G. Graham, C.S. Houston, Short-term adaptation to moderate altitude. Patients with chronic obstructive pulmonary disease, JAMA. 240 (14) (1978) 1491–1494.

[10] H. Gong, D.P. Tashkin, E.Y. Lee, M.S. Simmons, Hypoxia-altitude simulation test. Evaluation of patients with chronic airway obstruction, Am. Rev. Respir. Dis. 130 (6) (1984) 980–986.

[11] T.D. Latshang, R.P.M. Tardent, M. Furian, D. Flueck, S.D. Segitz, S. Mueller-Mottet, et al., Sleep and breathing disturbances in patients with chronic obstructive pulmonary disease traveling to altitude: a randomized trial, Sleep 42 (1) (2019).

[12] M. Bisang, T.D. Latshang, M. Furian, S.S. Aeschbacher, F. H, M. Lichtblau, et al., Risk of cardiac arrhythmias in lowlanders with COPD travelling to high altitude. Randomized trial of nocturnal oxygen therapy, Respiration. 94 (1) (2017) 76–156.

[13] M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, et al., Standardisation of spirometry, Eur. Respir. J. 26 (2) (2005) 319–338.

[14] H.C. Bazett, An analysis of the time-relations of electrocardiograms, Ann. Noninvasive Electrocardiol. 2 (2) (1997) 177–194.

[15] M.E. van den Berg, B.H. Stricker, G.G. Brusselle, L. Lahousse, Chronic obstructive pulmonary disease and sudden cardiac death: a systematic review, Trends Cardiovasc Med. 26 (7) (2016) 606–613.

[16] U. Nilsson, A. Blomberg, B. Johansson, H. Backman, B. Eriksson, A. Lindberg, Ischemic ECG abnormalities are associated with an increased risk for death among subjects with COPD, also among those without known heart disease, Int J Chron Obstruct Pulmon Dis. 12 (2017) 2507–2514.

[17] L.E. Vanfleteren, F.M. Franssen, N.H. Uszko-Lencer, M.A. Spruit, M. Celis, A.P. Gorgels, et al., Frequency and relevance of ischemic electrocardiographic findings in patients with chronic obstructive pulmonary disease, Am. J. Cardiol. 108 (11) (2011) 1669–1674.

[18] M.J. Warnier, F.H. Rutten, M.E. Numans, J.A. Kors, H.L. Tan, A. de Boer, et al., Electrocardiographic characteristics of patients with chronic obstructive pulmonary disease, COPD. 10 (1) (2013) 62–71.

[19] B.D. Halperin, S. Sun, J. Zhuang, T. Droma, L.G. Moore, ECG observations in Tibetan and Han residents of Lhasa, J. Electrocardiol. 31 (3) (1998) 237–243.

[20] N.A. Sievi, C.F. Clarenbach, G. Camen, V.A. Rossi, A.J. van Gestel, M. Kohler, High prevalence of altered cardiac repolarization in patients with COPD, BMC Pulm Med. 14 (2014) 55.

[21] M.E. Tavel, C. Shaar, Relation between the electrocardiographic stress test and degree and location of myocardial ischemia, Am. J. Cardiol. 84 (2) (1999) 119–124.

[22] T.M. Rywik, F.C. O'Connor, N.S. Gittings, J.G. Wright, A.A. Khan, J.L. Fleg, Role of nondiagnostic exercise-induced ST-segment abnormalities in predicting future coronary events in asymptomatic volunteers, Circulation. 106 (22) (2002) 2787–2792.

[23] B.D. Levine, J.H. Zuckerman, deFilippi CR. Effect of high-altitude exposure in the elderly: the Tenth Mountain division study, Circulation. 96 (4) (1997) 1224–1232.

[24] J.P. Schmid, M. Noveanu, R. Gaillet, G. Hellige, A. Wahl, H. Saner, Safety and exercise tolerance of acute high altitude exposure (3454 m) among patients with coronary artery disease, Heart. 92 (7) (2006) 921–925.

[25] S.F. Rimoldi, C. Sartori, C. Seiler, E. Delacrétaz, H.P. Mattle, U. Scherrer, et al., High-altitude exposure in patients with cardiovascular disease: risk assessment and practical recommendations, Prog. Cardiovasc. Dis. 52 (6) (2010) 512–524.
[26] S. Savonitto, G. Cardellino, G. Doveri, S. Pernpruner, R. Bronzini, N. Milloz, et al., Effects of acute exposure to altitude (3,460 m) on blood pressure response to dynamic and isometric exercise in men with systemic hypertension, Am. J. Cardiol. 70 (18) (1992) 1493–1497.
[27] W. Schobersberger, P. Schmid, M. Lechleitner, S.P. von Duvillard, H. Hörtnagl, H.C. Gunga, et al., Austrian moderate altitude study 2000 (AMAS 2000). The effects of moderate altitude (1,700 m) on cardiovascular and metabolic variables in patients with metabolic syndrome, Eur. J. Appl. Physiol. 88 (6) (2003) 506–514.
[28] P. Agostoni, G. Cattadori, M. Guazzi, M. Bussotti, C. Conca, M. Lomanto, et al., Effects of simulated altitude-induced hypoxia on exercise capacity in patients with chronic heart failure, Am. J. Med. 109 (6) (2000) 450–455.
[29] C.A. Goudis, A.K. Konstantinidis, I.V. Ntalas, P. Korantzopoulos, Electrocardiographic abnormalities and cardiac arrhythmias in chronic obstructive pulmonary disease, Int. J. Cardiol. 199 (2015) 264–273.
[30] T. Konecny, J.Y. Park, K.R. Somers, D. Konecny, M. Orban, F. Soucek, et al., Relation of chronic obstructive pulmonary disease to atrial and ventricular arrhythmias, Am. J. Cardiol. 114 (2) (2014) 272–277.
[31] T. Konecny, K.R. Somers, J.Y. Park, A. John, M. Orban, R. Doshi, et al., Chronic obstructive pulmonary disease as a risk factor for ventricular arrhythmias independent of left ventricular function, Heart Rhythm. 15 (6) (2018) 832–838.
[32] R. Passman, A. Kadish, Polymorphic ventricular tachycardia, long Q-T syndrome, and torsades de pointes, Med Clin North Am. 85 (2) (2001) 321–341.
[33] A.G. Stewart, J.C. Waterhouse, P. Howard, The QTc interval, autonomic neuropathy and mortality in hypoxaemic COPD, Respir. Med. 89 (2) (1995) 79–84.
[34] R. Zulli, P. Donati, F. Nicosia, M. De Vecchi, C. Tantucci, G. Romanelli, et al., Increased QT dispersion: a negative prognostic finding in chronic obstructive pulmonary disease, Intern. Emerg. Med. 1 (4) (2006) 279–286.
[35] T.D. Latshang, B. Kaufmann, Y. Nussbaumer-Ochsner, S. Ulrich, M. Furian, M. Kohler, et al., Patients with obstructive sleep apnea have cardiac repolarization disturbances when travelling to altitude: randomized, Placebo-Controlled Trial of Acetazolamide, Sleep. 39 (9) (2016) 1631–1637.
[36] M.M. Ciccone, S. Favale, P. Scicchitano, F. Mangini, G. Mitacchione, F. Gadaleta, et al., Reversibility of the endothelial dysfunction after CPAP therapy in OSAS patients, Int. J. Cardiol. 158 (3) (2012) 383–386.
[37] U. Nilsson, I. Kanerud, U.B. Diamant, A. Blomberg, B. Eriksson, A. Lindberg, The prevalence of prolonged QTc increases by GOLD stage, and is associated with worse survival among subjects with COPD, Heart Lung 48 (2) (2019) 148–154.
[38] H.F. Armstrong, G.S. Lovasi, E.Z. Soliman, S.R. Heckbert, B.M. Psaty, J.H. Austin, et al., Lung function, percent emphysema, and QT duration: the multi-ethnic study of atherosclerosis (MESA) lung study, Respir. Med. 123 (2017) 1–7.
[39] U. Nilsson, B. Johansson, B. Eriksson, A. Blomberg, B. Lundbäck, A. Lindberg, Ischemic heart disease among subjects with and without chronic obstructive pulmonary disease–ECG-findings in a population-based cohort study, BMC Pulm Med. 15 (2015) 156.